

# Center for Ultrasonic Drug Delivery

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Center Director  
BYU

# CANCER: How BIG is this problem?

- 1.3 Million people in the USA have cancer
- Estimated cost in 2004: \$190B
- Direct medical costs '04: \$69B
- More than half of these are tumors

# Big 4 Cancers are Tumors

- Men: prostate, lung, colorectal, bladder
- Women: breast, lung, colorectal, uterine

These are organs that we don't want to cut away!

# How can we effectively treat tumors with anti-cancer drugs??

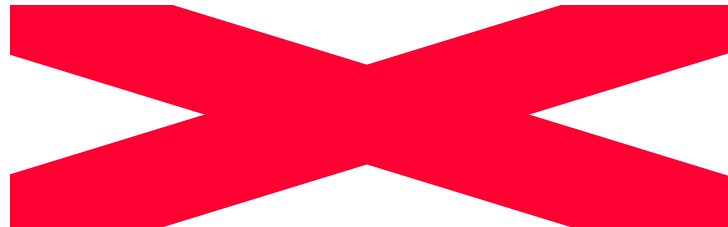
- Deliver high concentrations to a solid tumor inside the body
- Without side effects to the body
- Non-invasively (no cutting!)

# With site-specific drug delivery, which can:

- Avoid the knife! (no surgery)
- Treat the site only, not the rest of the body
- Avoid the side effects of chemotherapy

# How can our technology do it?

- We use ultrasound to release potent drugs from unique nanosized carriers
- Nanosized carriers sequester drug so it is not released to the rest of the body



# How do we do it?

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- Ultrasound is focused through the skin to irradiate the tumor only

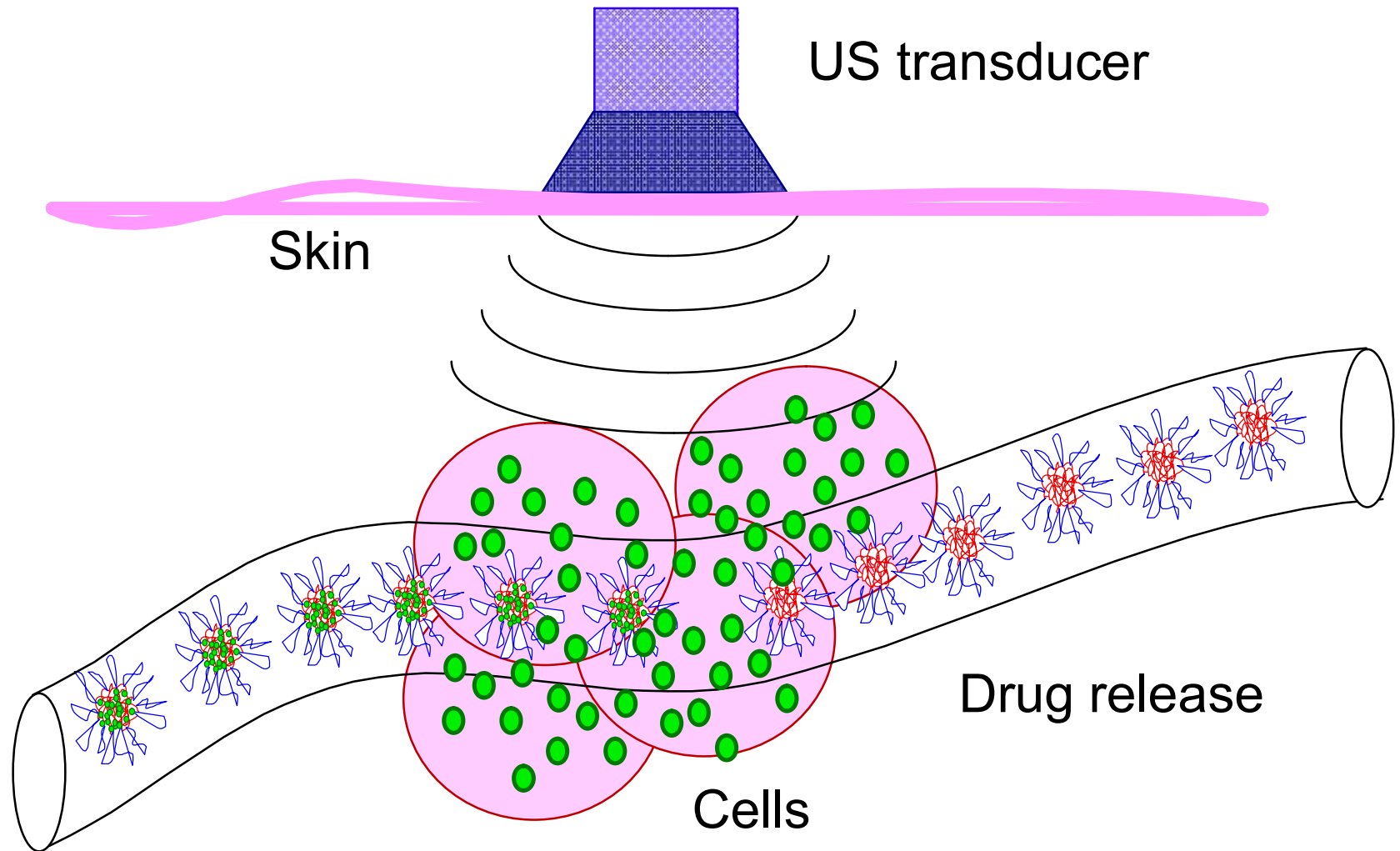
# Ultrasonic Transducer





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- Ultrasound is focused through the skin to irradiate the tumor only
- The drug carriers are opened by ultrasound, releasing the drug at the site only



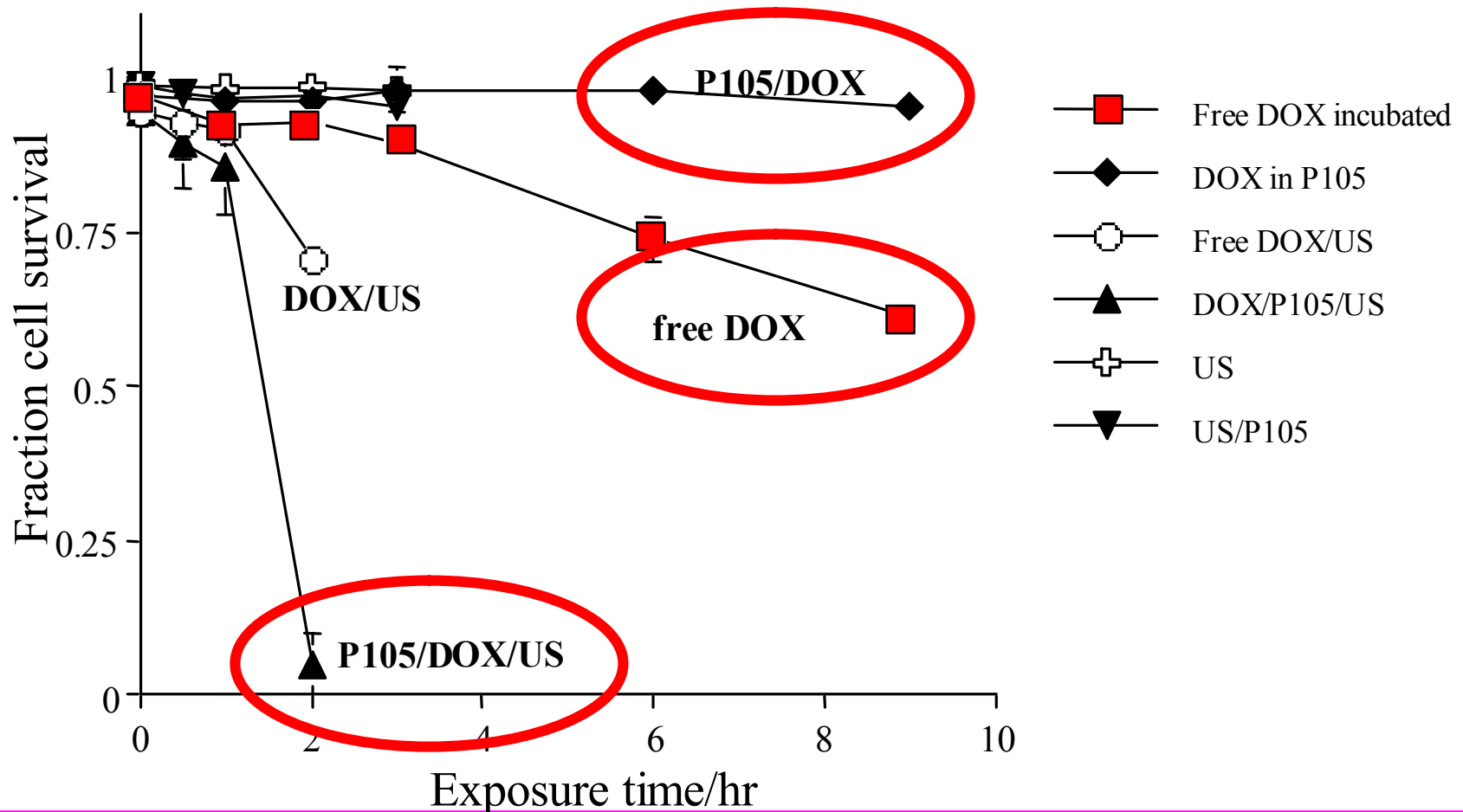
# Advantages of Ultrasound

- **Non-invasive, even to deep tissues**
- **Ultrasound can be focused**
- **Medically accepted and advanced technology**

# Where's the beef?



# In Vitro Cancer Cell Viability



# Animal Model

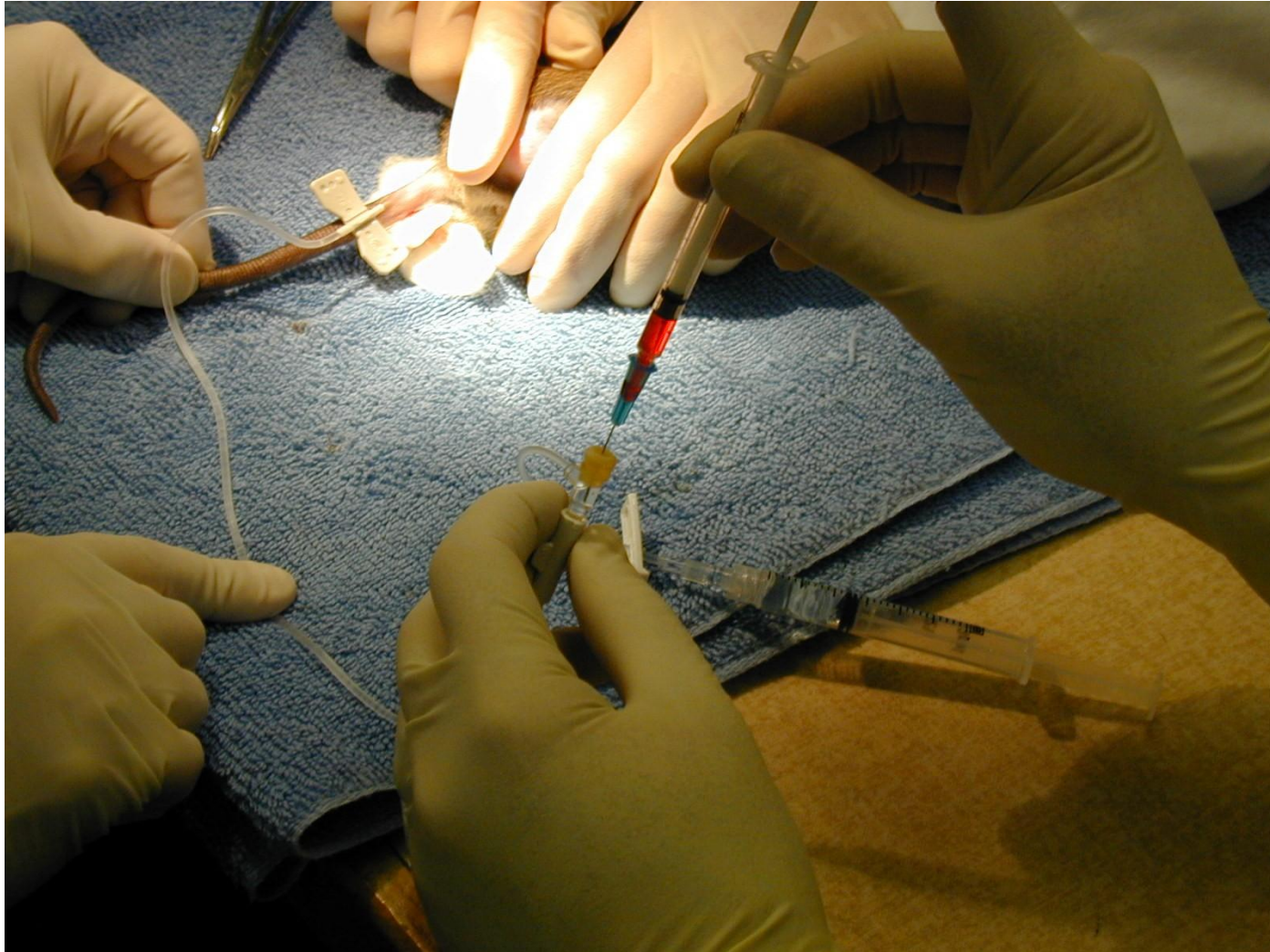
## ➤ BDIX Rat



- Two subcutaneous tumors were inoculated – one on each hind leg
- Systemic Doxorubicin (free or encapsulated)
- Ultrasound on one leg tumor only



# Drug Administration



# Ultrasound Application







Statistically, the ultrasonicated tumor was smaller or had regressed at 4 weeks ( $p=0.0062$ ,  $n=47$ )

# Why our approach is better

- Drug is released only where ultrasound is focused
- No side effects of chemotherapy
- Ultrasound is non-invasive and painless

# Intellectual Property

- 1 Patent on the process and on a drug carrier
- 2 patents pending on other drug carriers

# Market Interest

Inquiries from Kimberly  
Clark (Ogden and Sandy)  
and from EDO Acoustics  
(Salt Lake City)

# Project Plan

- License existing technology in year 1
- Prototype in year 2
- More animal trials in years 1-3
- Seek FDA approval for human studies in year 3
- Start clinical trials in year 4
- Continue to develop new technology in years 1-5

# Team Members

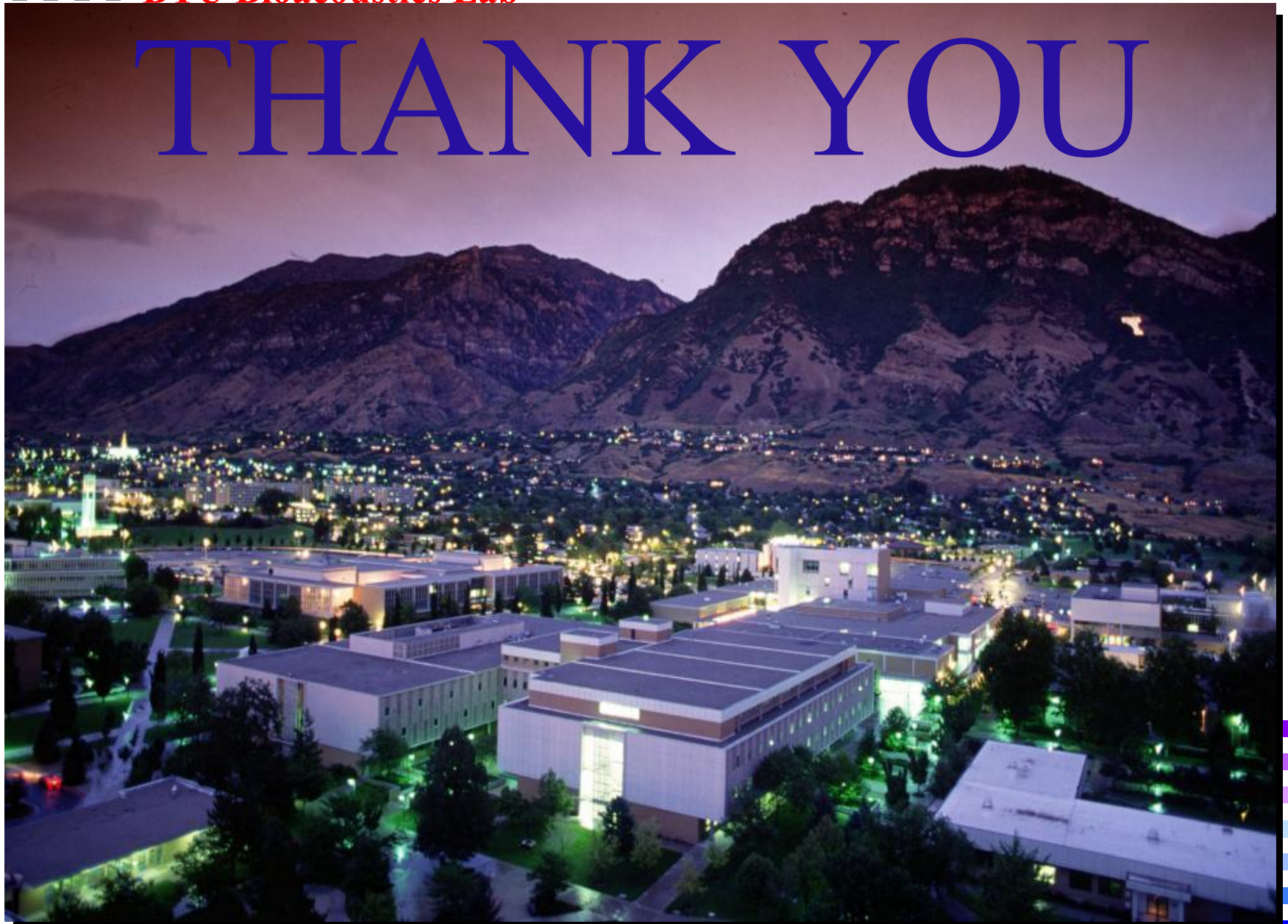
- Bill Pitt, BYU, Center Director
- Doug Christensen, UofU, ultrasonic technologies
- Byron Murray, BYU, cancer cell studies
- Beverly Roeder, BYU, animal studies
- Natasha Rapoport, UofU, drug carriers

# Funding Sources

- State Center Funds: \$108K year 1, \$124K in years 2 to 5
- Continuing NIH support of Dr. Pitt's lab
- Licensing royalties starting in year 2
- Some dues from membership in industrial consortium



# THANK YOU





# Center for Ultrasonic Drug Delivery

*A Better Way to  
Treat People*

# Patent

- N. Rapoport and W.G. Pitt, “Stabilization and Acoustic Activation of Polymeric Micelles for Drug Delivery”, a patent issued in the United States of America, November 18, 2003, Number 6,649,702.

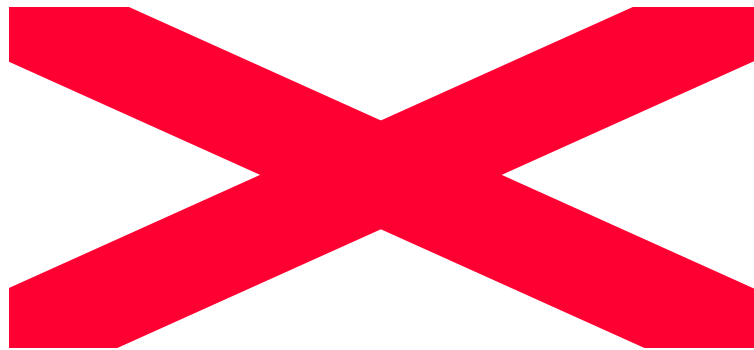
## Patents Pending

- W.G. Pitt, Y. Zeng, “Polymeric Nanoparticle with Controlled Lifetime”
- N. Rapoport and W.G. Pitt, “Ultrasonic Activation of Polymeric Micelles for Drug Delivery”

# Mission Statement

The mission of the Center for Ultrasonic Drug Delivery is to develop and transfer technology related to the use of non-invasive ultrasound to direct drug and gene delivery to specific target areas. This will enhance the health and comfort of patients undergoing chemotherapy and gene therapy.

# Timeline



# Development of Drug Carriers Responsive to Ultrasound

- Continue to improve on present chemistry
- Next generation of self-assembled micelles
- Extrinsic gas bubbles/carrier combos
- Micelles or lipospheres with biological targeting moieties

# Ultrasonic Physics

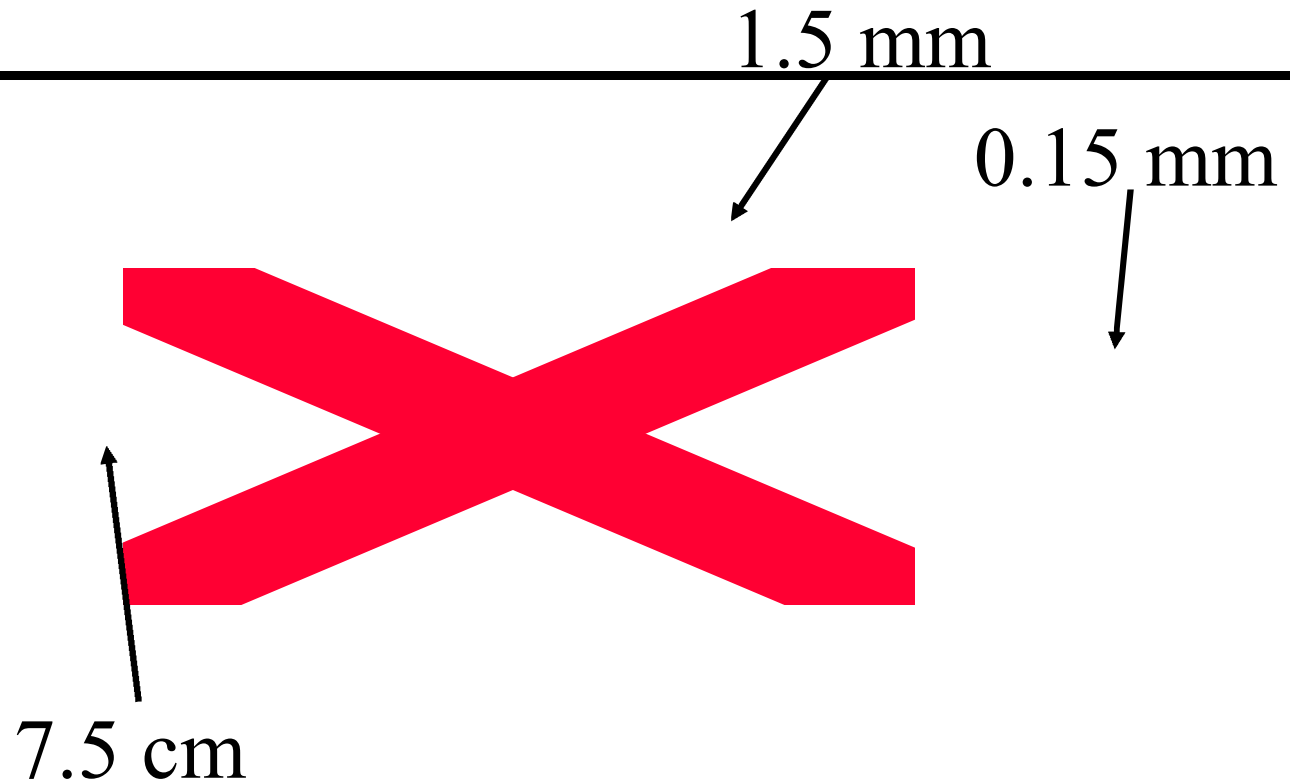
- Optimize acoustic parameters for drug delivery from various carriers
  - Frequency
  - Acoustic intensity
  - Pulse sequence
- Understand and optimize bubble cavitation phenomena
  - Bubble size and shell viscosity
  - Bubble density

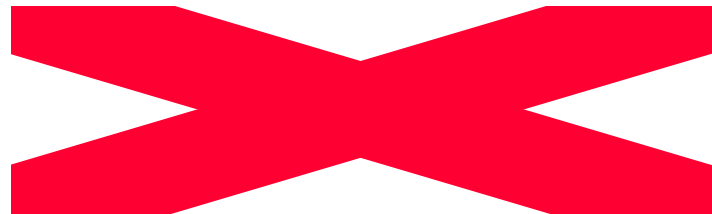
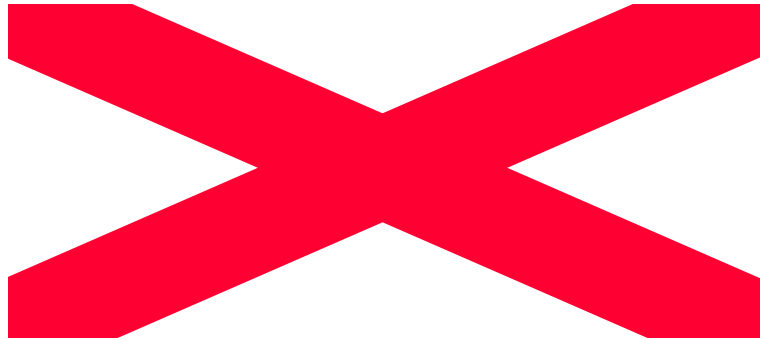
# Release of Doxorubicin from Pluronic



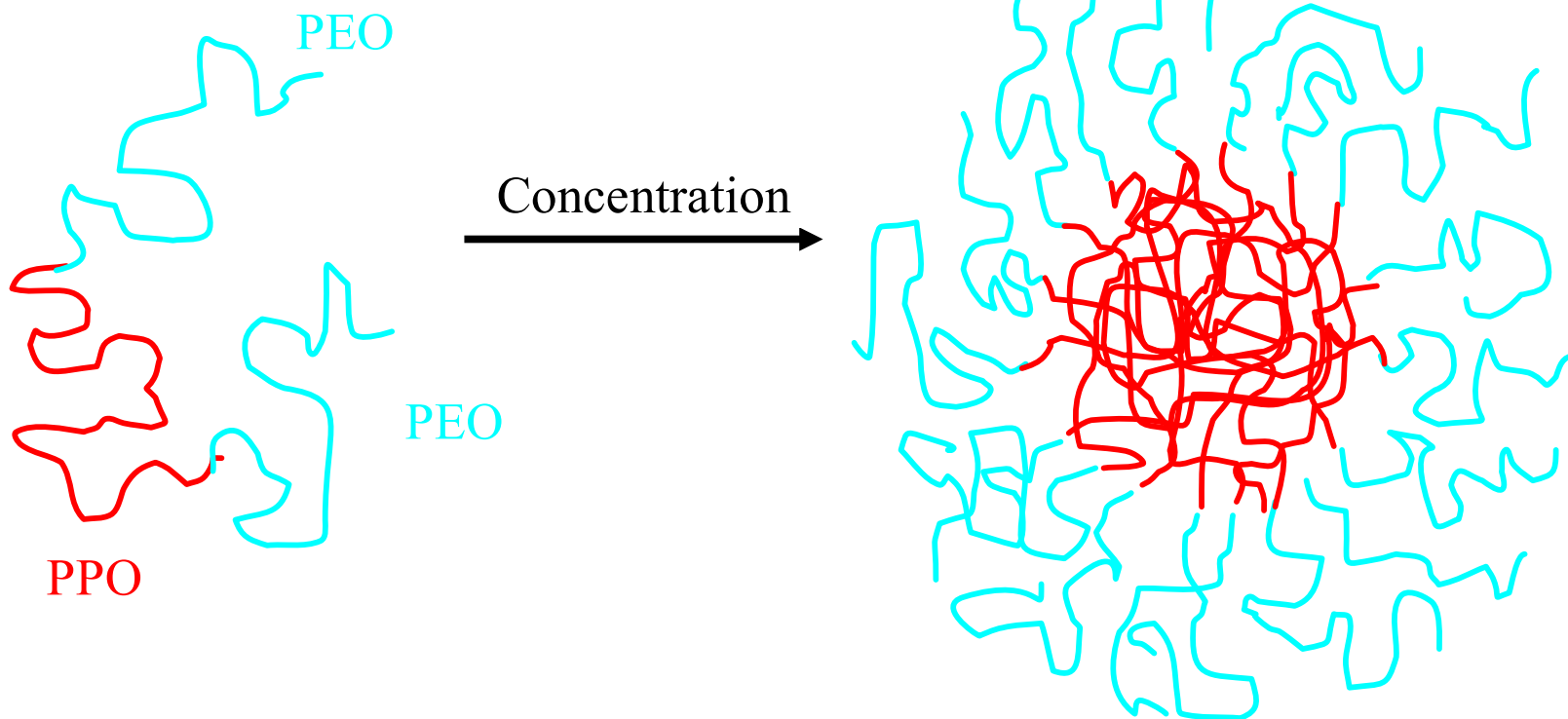
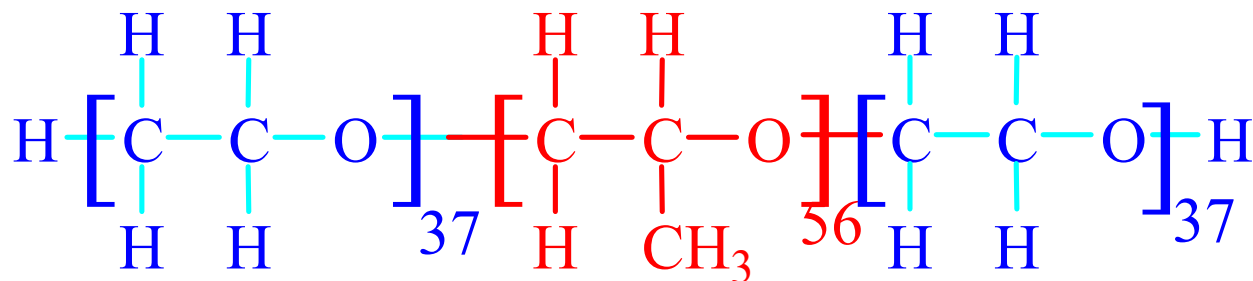


# Ultrasonic Wavelengths

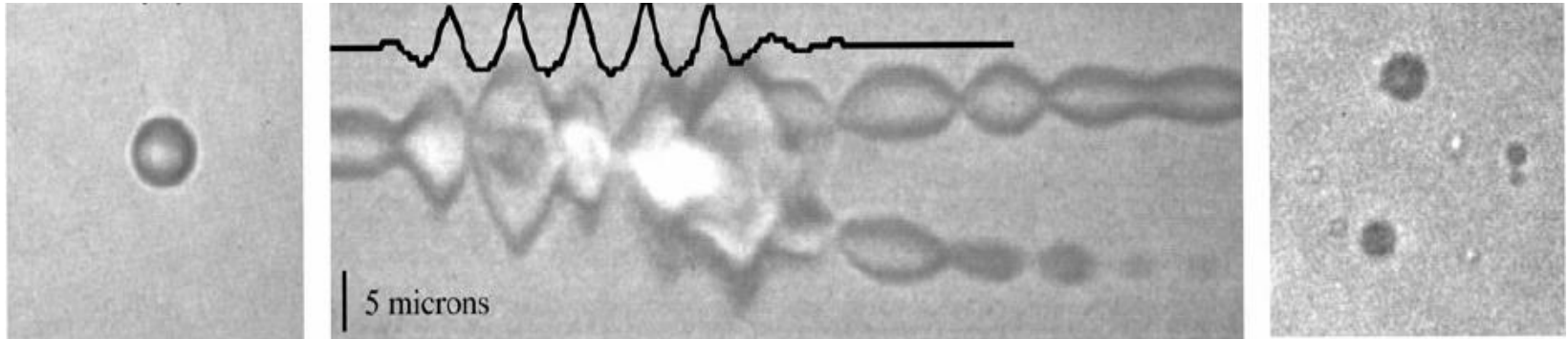




# Pluronic P-105



# Cavitation in Action



- Collapse cavitation is usually avoided in diagnostic US
- Collapse cavitation is usually the desired event in low frequency US
- Cavitation permeabilizes cells to drugs
- Cavitation releases drugs from carriers

# Past Work in Pitt's Lab

- Ultrasound to delivery antibiotics to implant infections
- Ultrasound for chemotherapeutic drug delivery
- Synthesis of novel carriers
- Patents

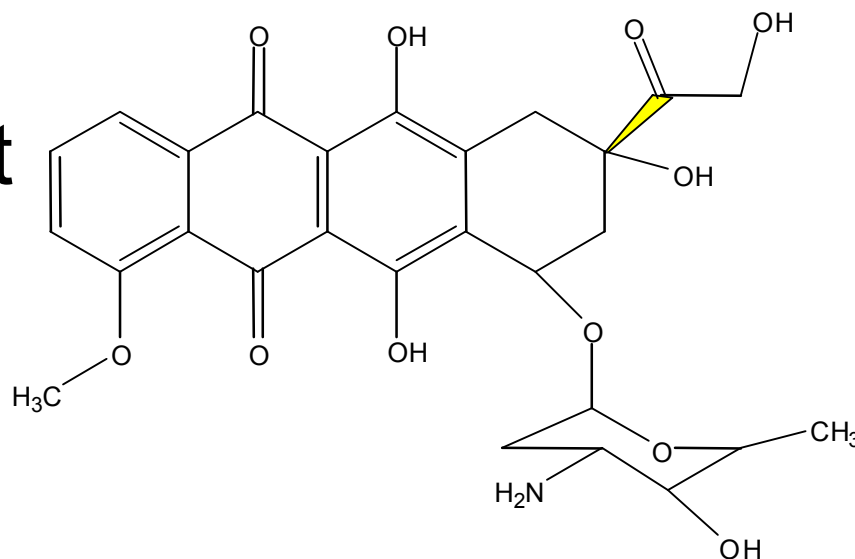


# Micellar Drug Delivery

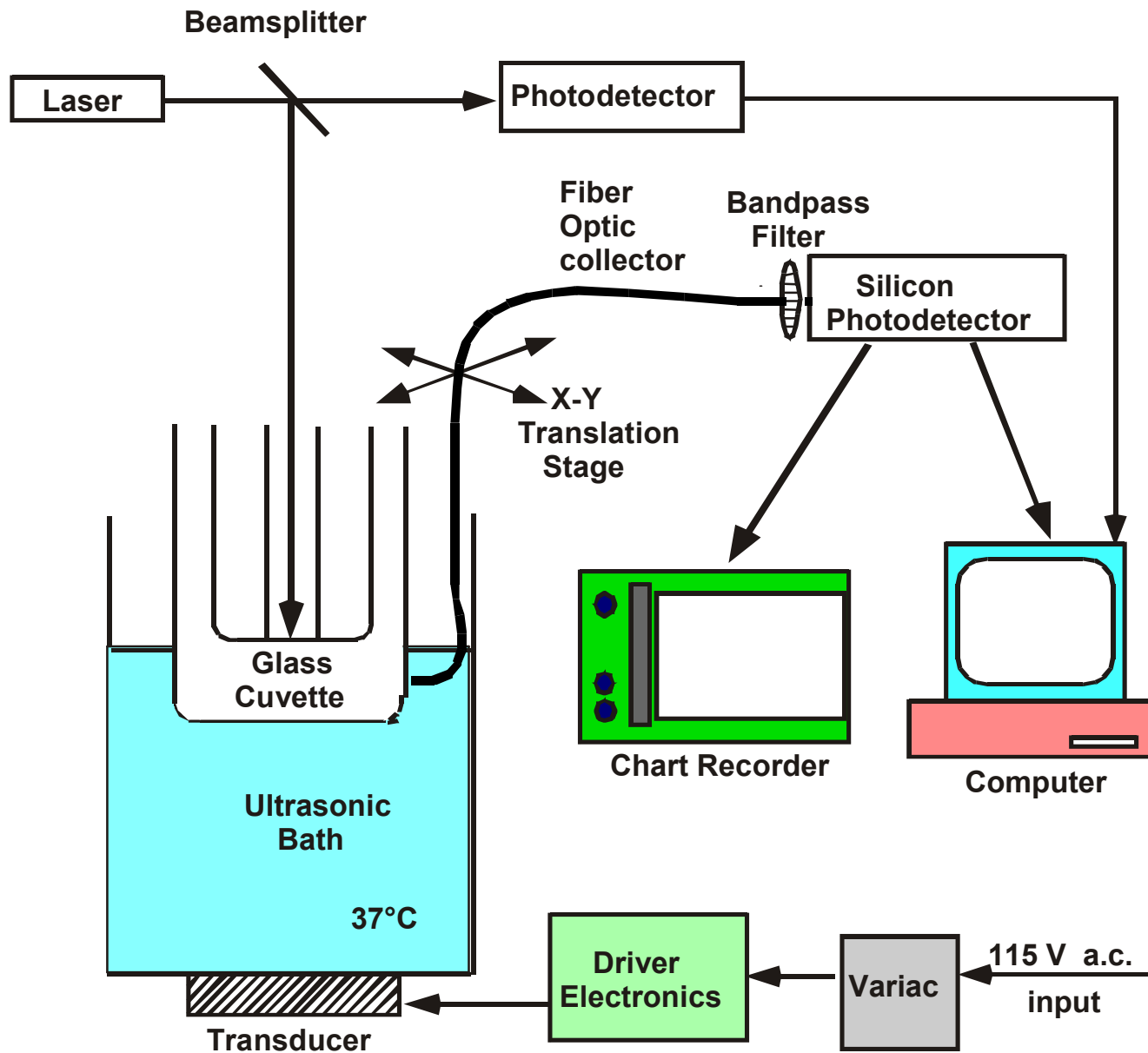
- In water at high concentrations, micelles spontaneously form
- Hydrophobic drugs partition inside
- Advantage is self assembly and small size
- Major drawback is stability of the micelles upon dilution
- Advantage is that collapse cavitation shears open micelles and releases drugs

# Ultrasonic Release of Doxorubicin

- Potent hydrophobic anti-cancer drug
- Intercalates DNA and interferes with replication, leading to breaks in DNA
- Cardiotoxic
- Dox is fluorescent







# Results

Growth followed one of two patterns

The insonated tumor continues to grow, but less than non-insonated tumor

The insonated tumor stopped growing or regressed

$P = 0.0062$  for significance that insonated tumors are smaller after 4 weeks treatment

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# Synthesis of US-responsive Drug Carriers

- Plurogel™
  - Used in many in vitro and in vivo expts
- Two new stabilized carriers
  - PEO-p(NIPAAm)
  - PEO-p(NIPAAm)-p(HEMA)-polylactate

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# Develop Ultrasonic Hardware with Drug Releasing Capabilities

- Low frequency focused ultrasound
- Dual frequency for imaging and drug release
- Industrial Partners
  - EDO Acoustics (Salt Lake)
  - Ballard Medical (Draper)
  - Kimberly Clark (Ogden)

# Spin Off Technology to Utah Businesses

- Ballard
- EDO
- Kimberly Clark
- ZEVEX and others

# Synergism and Leverage

- Currently we have a large NIH grant to study the physics of US/cavitation activated drug release from micelles
- We need hardware development for low frequency
- Kimberly Clark/Ballard have low frequency technology that they want to put into a medical application



## More Synergism

- There are many drug companies in the SLC area (spin offs from U of U and past COEs) that have novel drugs. We have a novel drug delivery system.
- Combination of specific ligand receptor systems with ultrasonically-activated drug carriers may be ideal for some of these companies.